

Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Currently amended) A compound of the structure or formula $S-(L)_n-B$ wherein:

- (a) S is an amino terminal signaling functional domain of PTH;
- (b) L is a linker molecule present n times; and
- (c) B is a carboxy terminal binding domain of PTH(1-34) or PTHrP(1-34),
wherein said carboxy terminal binding domain binds to a PTH-receptor 1 molecule

wherein said compound ~~is biologically active~~ has a biological activity substantially similar to PTH(1-34) or PTHrP(1-34) ; and

wherein said linker is selected from the group comprising an amino acid and an aliphatic diamine.

2. (Original) The compound of claim 1, wherein said compound is an isolated polypeptide.

3. (Original) The isolated polypeptide of claim 2 wherein n is 1-9.

4. (Original) The isolated polypeptide of claim 2, wherein S is selected from the group consisting of PTH(1-9)(Ala Val Ser Glu Ile Gln Leu Met His (SEQ ID NO: 1), PTH(1-

5)(Ala Val Ser Glu Ile (SEQ ID NO: 4) or PTH (1-11) (Ala Val Ser Glu Ile Gln Leu Met His Asn Leu (SEQ ID NO: 46).

5. (Previously presented) The isolated polypeptide of claim 2, wherein L is selected from the group consisting of Gly₅, Gly₇ and Gly₉.

6. (Previously presented) The isolated polypeptide of claim 2, wherein B is selected from the group consisting of PTH(15-31) (Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val) (SEQ ID NO:2), PTH(17-31) (Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val) (SEQ ID NO:63), PTHrP (15-31) (Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile) (SEQ ID NO:8), and PTHrP(17-31) (Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile) (SEQ ID NO:12).

7. (Previously presented) The isolated polypeptide of claim 2 selected from the group consisting of PG5: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:3), PG9: Ala Val Ser Glu Ile Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:5), PG7: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Gly Gly Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:6), PrPG5: Ala Val Ser Glu His Gln Leu Leu His Gly Gly Gly Gly Gly Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:64), PrPG9: Ala Val Ser Glu His Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly (Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu Ile (SEQ ID NO:65) and PrPG7: Ala Val Ser Glu His

Gln Leu Leu His Gly Gly Gly Gly Gly Gly Gly Asp Leu Arg Arg Arg Phe Phe Leu His His
Leu Ile Ala Glu Ile (SEQ ID NO:66) and functional derivatives thereof.

8. (Previously presented) The isolated polypeptide of claim 2 selected from the group consisting of PG5: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:3), PG9: Ala Val Ser Glu Ile Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:5), PG7: Ala Val Ser Glu Ile Gln Leu Met His Gly Gly Gly Gly Gly Gly Gly Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val (SEQ ID NO:6), and functional derivatives thereof.

9. (Original) The isolated polypeptide of claim 8 wherein there is a single amino acid substitution.

10. (Currently amended) The isolated polypeptide of claim 2, wherein:

(a) S is X Val X Glu X X X X His (SEQ ID NO: 42), wherein X is an amino acid; and

(b) L is 5-10 glycine residues; and

~~(c) B is X X X X X Arg X X Trp X Leu X Lys Leu X X Val (SEQ ID NO: 43), wherein X is an amino acid.~~

11. (Previously presented) The isolated polypeptide of claim 2, wherein:

(a) S is Ser Val Ser Glu Ile Gln Leu Met His (SEQ ID NO: 44);

- (b) L is 5-10 glycine residues; and
- (c) B is Leu Asn Ser Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln
Asp Val (SEQ ID NO: 45).

12. Cancelled.

13. Cancelled.

14. (Previously presented) The isolated polypeptide of claim 2, encoded by a nucleic acid sequence selected from the group consisting of: SEQ ID NO:14, SEQ ID NO:15 and SEQ ID NO:16.

15. (Withdrawn) An isolated nucleic acid sequence encoding the polypeptide of any one of claims 2-13.

16. (Withdrawn) An isolated polypeptide of the structure of formula $R_1-S-(L)_n-R$, or $S-(L)_n-R$ wherein:

- (a) R_1 is the PTH-1 receptor signal sequence;
- (b) S is an amino-terminal ligand signaling peptide;
- (c) L is a linker molecule present n times, where n is a positive integer 1-10, most preferably 4; and
- (d) R is PTH-1 receptor sequence or a portion of the receptor sequence.

17. (Withdrawn) The isolated polypeptide of claim 16, wherein R_1 is the PTH-1 receptor(1-25) peptide, S is the PTH(1-9) peptide, L is Gly, wherein N is 4; and R is the PTH-1 receptor (182-end).

18. (Withdrawn) The isolated polypeptide of claim 16 having the the formula $S-(L)_n-R$, wherein the R_1 moiety has been cleaved.

19. (Withdrawn) An isolated nucleic acid sequence encoding the polypeptide of claim 16.

20. (Withdrawn) An isolated polypeptide of the formula S-R, wherein:

- (a) S is an amino-terminal signaling polypeptide; and
- (b) R is a carboxy-terminal receptor polypeptide.

21. (Withdrawn) The isolated polypeptide of Claim 20, wherein S is the amino-terminal signaling polypeptide X Val X Glu X X X X His, wherein X is an amino acid.

22. (Withdrawn) An isolated polypeptide comprising a sequence selected from the group the of sequences consisting of SEQ ID NO: 37, SEQ ID NO:39 and SEQ ID NO: 41.

23. (Withdrawn) An isolated nucleic acid sequence encoding a polypeptide sequence of claim 22.

24. (Withdrawn) An isolated nucleic acid sequence selected from the group consisting of SEQ ID NO:36, SEQ ID NO:38 and SEQ ID NO:40.
25. (Withdrawn) An isolated nucleic acid sequence, wherein said sequence is at least 95% identical to or binds under stringent conditions to a sequence of claim 24.
26. (Withdrawn) A recombinant vector comprising a nucleic acid sequence of claim 15
27. (Withdrawn) A recombinant host cell comprising the DNA of claim 26.
28. (Withdrawn) A recombinant vector comprising a nucleic acid sequence of claim 23.
29. (Withdrawn) A recombinant host cell comprising the DNA of claim 28.
30. (Withdrawn) A method for treating mammalian conditions characterized by decreases in bone mass, wherein said method comprises administering to a subject in need thereof an effective bone mass-increasing amount of the polypeptide of any one of claims 2, 16 or 20.
31. (Withdrawn) A method for determining rates of bone reformation, bone resorption and/or bone remodeling comprising administering to a patient an effective amount

of a polypeptide of any one of claims 2, 20 or 40 and determining the uptake of said peptide into the bone of said patient.

32. (Withdrawn) The method of claim 30, wherein said effective bone mass-increasing amount of said peptide is administered by providing to the patient DNA encoding said peptide and expressing said peptide *in vivo*.

33. (Withdrawn) The method of claim 32, wherein the condition to be treated is osteoporosis.

34. (Withdrawn) The method of claim 24, wherein the effective amount of said polypeptide for increasing bone mass is from about 0.01 µg/kg/day to about 1.0 µg/kg/day.

35. (Withdrawn) A method of treating diseases and disorders associated with decreased Tether1 activity comprising administering an effective amount of the polypeptide of any one of claims 2, 20 or 40, or an agonist thereof to a patient in need thereof.

36. (Withdrawn) A method of increasing cAMP in a mammalian cell having PTH-1 receptors, comprising contacting said cell with a sufficient amount of the polypeptide of any one of claims 2, 20 or 40 to increase cAMP.

37. (Original) The isolated polypeptide of claim 2 wherein B is 10-20 amino acids in length.

38. (Withdrawn) A method for screening for a peptide or non-peptide PTH agonist comprising:

- (a) binding a polypeptide of claim 16 to a potential agonist; and
- (b) isolating said potential agonist from said polypeptide.

39. (Withdrawn) The method of claim 38, wherein said polypeptide is Tether 1 or rδNt.

40. (Withdrawn) An isolated polypeptide, wherein said polypeptide is obtained by the method of claim 38.

41. (New) The compound of claim 1, wherein said aliphatic diamine comprises 1 to 6 carbons.

42. (New) The compound of claim 41, wherein said aliphatic diamine is selected from the group consisting of methylene diamine, ethylene diamine, propylene diamine, tetramethylene diamine, pentamethylene diamine, hexamethylene diamine, tetramethylene diamine (also known as cadaverine), pentamethylene diamine (also known as putrescine, hereinafter Pu), and hexamethylene diamine.